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(71) Applicant
Farmitalia Carlo Erba S.r.l.

(incorporated in Italy)

Via Carlo Imbonati 24, 20159, Italy

(72) Inventors
Federico Spreafico
Nicola Mongelli
Roberto D'Alessio
Maria Grandi

(74) Agent and/or Address for Service
J A Kemp and Co
14 South Square, Gray's Inn, London, WC1R 5LX, United Kingdom

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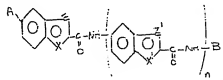
(58) Field of search
Online databases: CAS ONLINE

(54) Heterocyclic oligopeptides endowed with antitumour activity

(57) Heterocyclic oligopeptide derivatives of formula:



(I)

[wherein A is hydrogen, –NHCOR$_1$ (in which R$_1$ is an acrylic group substituted in 2-position by halogen, oxiranyl (unsubstituted or substituted in 2- or 3- position by a methyl), aziridinyl, cyclopropyl, 4–[N,N–bis–(2–chloroethyl)amino] phenyl, an alicyclic α, β–unsaturated ketone or a lactone) or

(in which R$_2$ and R$_3$ have both the same meaning

of a C$_2$–C$_4$ alkyl group substituted in 2-position by halogen or by a group –OSO$_2$R$_4$ (in which R$_4$ is C$_2$–C$_4$ alkyl or phenyl group), or one of R$_2$ and R$_3$ is hydrogen and the other has the meaning as defined above);

B is

hydrogen or –(CH$_2$)$_m$NHCOR$_1$ (in which R$_1$ is as defined above and m has the value of zero or is an integer from 1 to 3);

provided that when A is hydrogen, B is other than hydrogen, and that when A has the other meanings as defined above except hydrogen, B is only hydrogen; each Z and Z' is, independently, –CH= or –CH=CH–; each of X and X' is, independently, N, O or S; and n is zero or 1] and their isomers and pharmaceutically acceptable salts, show *cytostatic properties* towards tumour cells.

Also disclosed are pharmaceutical compositions containing as active substance a compound of formula I and methods of preparing such compounds. Intermediate products of formula (II), (IV) and (VI) are also disclosed (see claims 6,7 & 8).

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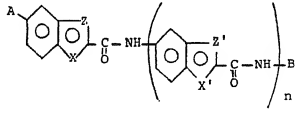
HETEROCYCLIC OLIGOPEPTIDES ENDOWED WITH ANTITUMOR ACTIVITY

The invention relates to heterocyclic oligopeptide derivatives having cytostatic properties towards tumour cells, as well as to methods for their preparation, to intermediate products and to pharmaceutical compositions containing them.

The compounds of the present invention are represented by the formula:



(I)

wherein A is hydrogen; $-NHCOR_1$ in which R_1 is an acrylic group substituted in 2-position by halogen, oxiranyl unsubstituted or substituted in 2- or 3-position by a methyl, aziridinyl, cyclopropyl, 4-[N,N-bis-(2-chloroethyl)amino]phenyl, an alicyclic α,β-unsaturated ketone or a lactone;

$-N\begin{matrix}R_2\\ \diagup\\ \diagdown\\ R_3\end{matrix}$ in which R_2 and R_3 have both the same meaning of C_2-C_4 alkyl group substituted in 2-position by halogen or by a group $-OSO_2R_4$, in which R_4 is C_2-C_4 alkyl or phenyl group, or one of R_2 and R_3 is hydrogen and the other has the meaning as defined above;

B is

hydrogen; $-(CH_2)_mNHCOR_1$, in which R_1 is as defined above and m has the value of zero or is an integer from 1 to 3;

provided that when A is hydrogen, B is other than hydrogen, and that when A has the other meanings as defined above except hydrogen, B is only hydrogen;

each Z and Z' is, indipendently, -CH= or -CH=CH-;

each of X and X' is, indipendently, N, O or S;

and n is zero or 1.

Preferred meanings of the substituents of compounds of formula (I) are:

R_1 = 2-bromoacrylyl, oxiranyl, 4-[N,N-bis(2-chloroethyl)amino]phenyl;

m = zero or 2;

R_2 and R_3 = a C_2-C_4 alkyl group substituted in 2-position by halogen such as 2-chloro-

ethyl, or by a group $-OSO_2R_4$, such as $-CH_2-CH_2-OSO_2R_4$ wherein R_4 is, preferably, methyl;

Z' = -CH=;

each of X and X' is, indipendently, nitrogen or oxygen;

n = 1.

A preferred class of compounds of the invention is represented by the compounds of formula (I) wherein:

A is hydrogen;

B is $-(CH_2)_mNHCOR_1$ wherein R_1 is 2-bromoacrylyl, oxiranyl or 4-[N,N-bis(2-chloroethyl)amino]phenyl and m is zero or 2;

Z is -CH= when X is oxygen or -CH=CH- when X is nitrogen; Z' is -CH= and X' is nitrogen; n is zero or 1.

Another preferred class of compounds of the invention is represented by the compounds of formula (I) wherein:

A is $-NHCOR_1$ in which R_1 is 2-bromoacrylyl, oxiranyl, 4-[N,N-bis(2-chloroethyl)amino]-phenyl

in which R_2 and R_3 are the same and when they are a C_2-C_4 alkyl groups substituted in 2-position by halogen, they are preferably 2-chloroethyl;

Z and Z' are both -CH=;

X and X' are both nitrogen;

B is hydrogen;

n is 1.

Specific examples of preferred compounds under this invention are the following:

2'-(α-bromoacryloyl)-5-(benzofuran-2-carboxamido)-indole-2-carbohydrazide;

2'-(2,3-epoxypropionyl)-5-(benzofuran-2-carboxamido)-indole-2-carbohydrazide;

2'-[4-(N,N-bis-2'-chloroethylamino)benzoyl]-5-(benzofuran-2-carboxamido)indole-2-carbohydrazide;

2'-(α-bromoacryloyl)-5-(quinoline-2-carboxamido)-indole-2-carbohydrazide;

2'-(2,3-epoxypropionyl)-5-(quinoline-2-carboxamido)-indole-2-carbohydrazide;

2'-[4-(N,N-bis-2'chloroethylamino)benzoyl]-5-(quinoline-2-carboxamido)indole-2-carbohydrazide;

5-[5-[4-[N,N-bis(2-chloroethyl)amino]benzoylamino]-

indole-2-carboxamido/-indole-2-carboxamide;

5-/5-(2,3-epoxypropionylamino)indole-2-carboxamido/ indole-2-carboxamide;

5-/5-(α -bromoacryloylamino)indole-2-carboxamido/-indole-2-carboxamide;

5-/5-/N,N-bis(2-chloroethyl)amino/indole-2-carboxamido/indole-2-carboxamide;

N-/2-/4-/N,N-bis(2-chloroethyl)amino/benzoylamino/--ethyl/-5-/benzofuran-2-carboxamido/indole-2-carboxamide;

N-/2-(2,3-epoxypropionylamino)ethyl/-5-/benzofuran -2-carboxamido/indole-2-carboxamide;

N-/2-(α-bromoacriloylamino)ethyl/-5-/benzofuran-2--carboxamido/indole-2-carboxamide;

N-/2-/4-/N,N-bis(2-chloroethyl)amino/benzoylamino/--ethyl/-5-/quinoline-2-carboxamido/indole-2--carboxamide;

N-/2-(2,3-epoxypropionylamino)ethyl/-5-/quinoline 2-carboxamido/indole-2-carboxamide;

N-/2-(α -bromoacryloylamino)ethyl/-5-/quinoline-2--carboxamido/indole-2-carboxamide;

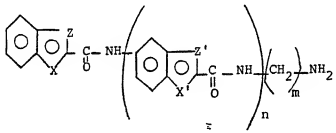
N-/2-/4-/N,N-bis(2-chloroethyl)amino/benzoylamino/-ethyl/quinoline-2-carboxamide;

N-/2-(2,3-epoxypropionylamino)ethyl/quinoline-2-carboxamide;

N-[2-(α-bromoacryloylamino)ethyl]quinoline-2-carboxamide.

This invention includes also the pharmaceutically acceptable salts of the compounds of formula (I), as well as their possible isomers both separately and in mixture. The term "pharmaceutically acceptable salts" includes the salts with pharmaceutically acceptable acids, either inorganic acids such as hydrochloric, hydrobromic, nitric and sulfuric acid, or organic acids such as citric, tartaric, maleic, fumaric, methanesulfonic and ethanesulfonic acid.

Another object of the present invention relates to methods to prepare compounds of formula (I). The compounds of formula (I) in which A is hydrogen and B is $-(CH_2)_mNHCOR_1$ wherein R_1 and m are as defined above can be prepared by reacting a compound of formula:

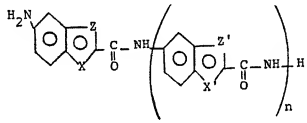


(II)

wherein X, X', Z, Z', m and n are as defined above, with a compound of formula:

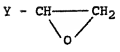
(III)

wherein R_1 is as defined above and L represents a leaving group such as halogen like chlorine or bromine, an imidazolyl, a pivaloyloxy or isobutyloxycarbonyloxy group. The compound of formula (III) can also be reacted with a compound of formula:



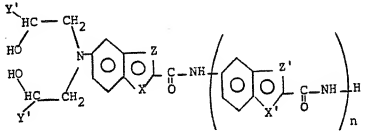
(IV)

wherein X, X', Z, Z' and n are as defined above, with a compound of formula (III), in order to obtain a compound of formula (I) wherein B is hydrogen, A is $-NHCOR_1$ in which R_1, is a defined above and X, X', Z, Z' and n are as defined above; the compound of formula (IV) can also be reacted with a compound of formula:



(V)

wherein Y is hydrogen or a C_1-C_2 alkyl group, to obtain a compound of formula



(VI)

wherein X, X', Z, Z', and n are as defined above and Y' has the same meaning of Y, which can be transformed into a compound of formula (I) wherein B is hydrogen, A is

in which R_2 and R_3 are as defined above and X, X', Z, Z' and n are as defined above;

a compound of formula (I) can optionally be converted into another compound of the same formula, and optionally, transformed, into one of their pharmaceutically acceptable salts.

The reaction between a compound of formula (II)

or (IV) and a compound of formula (III) is preferably carried out in the presence of a solvent and, preferably, using an excess of the compound of formula (III) in ratio of from 1.1 to 2 moles of compound (III) to 1 mole of compound of formula (II) or (IV).

The solvent is, preferably, an inert organic solvent chosen from dialkylsulphoxides such as dimethylsulphoxide, aliphatic acid, dialkylamides such as dimethylformamide, heterocyclic amines such as pyridine, aliphatic alcohols or water. A particularly preferred solvent is dimethylformamide. The reaction temperature may range from about 20°C to about 80°C. The time required for the reaction may vary approximately within a range from 0.5 to 24 h.

The reaction between a compound of formula (IV) and a compound of formula (V) is preferably carried out in the presence of a solvent and preferably using an excess of the compound of formula (V) in ratio of from 25 moles to 50 moles of compound (V) to 1 mole of compound (IV). The solvent may be water, an aliphatic alcohol such as methanol or ethanol, an aliphatic carboxylic acid such as acetic acid, an aliphatic acid dialkylamide such as

dimethylformamide, a dialkylsulphoxide such as dimethylsulphoxide, dioxane or dimethoxyethane. A particularly preferred solvent is methanol. The reaction temperature may range from about -20°C to about 25°C. The time required for the reaction may vary within a range from about 2 to about 48 h.

The transformation of a compound of formula (VI) into a compound of formula (I) wherein

A is  in which R_2 and R_3 are as defined

above, is carried out through reaction commonly used in organic chemistry. Thus for example, a compound of formula (VI) may be reacted with a halogenating agent such as chlorine, bromine, a thionyl halide such as thionyl chloride, or a sulphonyl halide such as methanesulphonyl chloride, to give a compound of formula (I).

Similarly a compound of formula (VI) may be reacted with a sulphonic acid of formula R_4SO_3H, wherein R_4 is as defined above or, more preferably with a reactive derivative thereof such as the corresponding sulphonyl halide like sulphonyl chloride or anhydride, to give a compound of formula (I).

Also the optional conversion of a compound of formula (I) into another compound of formula (I), the optional salification of a compound of formula (I) and the optional preparation of a free compound from a salt may be carried out according to known methods. Fractional crystallization and chromatography, used for separating a mixture of isomers of formula (I) into single isomers, are carried out by conventional procedures.

Another aspect of the present invention relates to the intermediate products of formula (II), (IV) and (VI). These compounds are new and they can be prepared by following conventional amidation procedures starting either from commercially available compounds or from compounds prepared by known methods (J.A.C.S., 1958, 80, 4621). Compounds of formula (III) are known compounds and they can be prepared through activation of the carboxy parent compounds in a conventional way and compounds of formula (V) are commercially available compounds.

The compounds of the invention of formula (I) show cytostatic properties towards tumour cells so that they can be useful, e.g., to inhibit the growth of various tumours, such as, for instance,

carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma; colon carcinoma, ovary and endometrial tumors. Other neoplasias in which the compounds of the invention could find application are, for instance, sarcomas, e.g. soft tissue and bone sarcomas, and the hematological malignancies such as, e.g., leukemias.

Tables 1 and 2 illustrate the cytostatic properties towards tumour cells of products of the present invention.

TABLE-1

Antitumor activity of 2'-(α-bromoacryloyl)-5-(benzofuran-2-carboxamido)indole-2-carbohydrazide

Tumour cells	IC_{50}(γ/ml)
L 1210	0.188
L 1210/LPAM	0.188
LOVO	0.478
LOVO/D	0.500

TABLE 2

Antitumor activity of 2'-[4-(N,N-bis-2'-chloroethylamino-benzoyl]-5-[benzofuran-2-carboxamido]-indole-2-carbohydrazide

Tumour cells	IC_{50} (γ/ml)
L 1210	1.45
L 1210/LPAM	1.40
LOVO	42

The compounds of the invention can be administered by the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally. The dosage depends on the age, weight and conditions of the patient and on the administration route. For example, a suitable dosage for administration to adult humans may range from about 0.1 to about 100 mg pro-dose 1-4 times a day.

The pharmaceutical compositions of the invention contain a compound of formula (I) as the active substance, in association with one or more pharmaceutically acceptable excipients. The pharmaceutical compositions of the invention are usually prepared following conventional methods and

are administered in a pharmaceutically suitable form. For instance, solutions for intravenous injection or infusion may contain as carrier, for example, sterile water or preferably, they may be in the form of sterile aqueous isotonic saline solutions. Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride. In the forms for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleaginous or emulsifyng excipients. The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g., lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethyl cellulose, polyvinylpyrrolidone; disaggregating agents, e.g. a starch, alginic acid,

alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactered in a known manner, for example by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

Furthemore, according to the invention there is provided a method of treating tumours in a patient in need of it, comprising administering to the said patient a composition of the invention.

In the following examples, the terms DMSO, THF and DMF stand, respectively, for dimethylsulphoxide, tetrahydrofuran and dimethylformamide. The following examples illustrate without limiting the invention.

EXAMPLE 1

To a stirred solution of 80% 2,3-epoxypropionic acid (132 mg) in DMF (3 ml) under nitrogen atmosphere, N,N-carbonyldiimidazole (194 mg) was added and the mixture allowed to stand at room temperature for 45 minutes and then treated with a

solution of 5-(benzofuran-2-carboxamido)indole-2-carbohydrazide (200 mg) in DMF (5 ml). After standing for one hour at room temperature the solution was poured into water and the white solid collected and washed with water to give 190 mg of 2'-(2,3-epoxypropionyl)-5-(benzofuran-2-carboxamido) indole-2-carbohydrazide,

NMR (DMSO-d_6) δ : 2.7-3.2 (2H,m); 3.53 (1H,dd); 7.21 (1H,bs); 7.25-8.10 (7H,m); 8.13 (1H,bs); 10.38 (3H,s); 11.7 (1H,bs).

By analogous procedure the following compounds were obtained:

2'-(2,3-epoxypropionyl)-5-(quinoline-2-carboxamido)-indole-2-carbohydrazide,

NMR (DMSO-d6) δ : 2.70-3.18 (2H,m); 3.52 (1H,dd); 7.10-8.80 (10H,m); 10.15-10.55 (2H,br); 10.65 (1H,s); 11.75 (1H,bs);

5-[5-(2,3-epoxypropionylamino)indole-2-carboxamido]-indole-2-carboxamide;

NMR (DMSO-d6) δ : 2.71-3.20 (2H,m); 3.5 (1H,dd); 6.8-8.2 (10H,m); 10.31 (2H,s); 11.55 (1H,bs); 12.09 (1H,bs);

N-[2-(2,3-epoxypropionylamino)ethyl]-5-[benzofu-

ran-2-carboxamido]indole-2-carboxamide;

NMR (DMSO-d6) δ : 2.6-2.95 (2H,m); 3.0-3.7 (5H,m);
6.9-8.25 (10H, m); 8-8.45 (1H, br);
10.3 (1H,s); 11.5 (1H, bs)

N-[2-(2,3-epoxypropionylamino)ethyl]-5-[quinoline-2
carboxamido]indole-2-carboxamide;

N-[2-(2,3-epoxypropionylamino)ethyl]quinoline-2-
carboxamide.

NMR(DMSO-d6) δ : 2.6-3.0 (2H, m); 3.05-3.80 (5H,m);
7.4-8.7 (7H, m); 8.95 (1H, bt).

EXAMPLE 2

To a stirred solution of 5-/5-aminoindole-2-carboxamido/indole-2-carboxamide hydrochloride (1 g) in methanol (150 ml), cooled to -10°C, cold ethylene oxide (15 ml) was added.

The reaction flask was sealed and allowed to stand at room temperature overnight. The methanol and the excess of ethylene oxide were removed under reduced pressure and the residue washed with ethyl acetate to give 860 mg of 5-[5-[N,N-bis(2-hydroxyethyl)amino]indole-2-carboxamido]indole-2-

carboxamide,

NMR (DMSO-d6) δ : 2.90-3.80 (8H,m); 6.9-8.2 (10H,m); 10.28 (1H,s); 11.54 (1H,bs); 12.09 (1H,bs).

EXAMPLE-3

A solution of 5-[5-[N,N-bis(2-hydroxyethyl)-amino]indole-2-carboxamido]indole-2-carboxamide (860 mg) in pyridine (10 ml), cooled to 0-5°C, was treated with methanesulphonyl chloride (0.34 ml) in pyridine (3 ml) for one hour. After addition of methanol (10 ml), the reaction mixture was warmed to room temperature. The solvents were removed *in vacuo* and the residue washed with acetone and collected to give 470 mg of 5-[5-[N,N-bis(2-chloro-ethyl)amino]indole-2-carboxamido]indole-2-carboxamide,

NMR (DMSO-d6) δ : 3.20-3.70 (8H,m); 6.9-8.25 (10H,m); 10.3 (1H,s); 11.54 (1H,bs); 11.8 (1H,bs).

EXAMPLE-4

To a stirred solution of 5-(benzofuran-2-carboxamido)indole-2-carbohydrazide (100 mg) in dry pyridine (1 ml), 4-[N,N-bis(2-chloroethyl)-amino]benzoyl chloride (100 mg) was added and the

solution allowed to stand at room temperature for 30 minutes. The mixture was poured into 2N hydrochloric acid and the residue collected and washed with acetone to give 2'-[4-(N,N-bis-2'-chloroethylamino)benzoyl]-5-(benzofuran-2-carboxamido)indole-2-carbohydrazide (150 mg) as a white solid,

NMR (DMSO-d6) δ : 3.4-4.1 (8H,m); 6.7-8.2 (13H,m); 10.2 (1H,s); 10.42 (2H,s); 11.7 (1H,s).

By analogous procedure the following compound were obtained:

2'-[4-(N,N-bis-2'-chloroethylamino)benzoyl]-5-(quinoline-2-carboxamido)indole-2-carbohydrazide;

NMR (DMSO-d6) δ :3.6-4.1 (8H, m); 6.7-8.75 (14H,m); 10.2 (1H,bs); 10.35 (1H,bs); 10.65 (1H,s); 11.7 (1H, bs).

5-[5-[4-[N,N-bis(2-chloroethyl)amino]benzoylamino]-indole-2-carboxamido]indole-2-carboxamide;

N-[2-[4-[N,N-bis(2-chloroethyl)amino]benzoylamino]-ethyl]-5-[benzofuran-2-carboxamido]indole-2-carboxamide;

NMR (DMSO-d6) δ: 3.1-3.55 (4H, m); 3.55-4.0 (8H,m); 6.6-8.7 (15H,m); 10.35 (1H,s); 11.55 (1H,bs).

N-[2-[4-[N,N-bis(2-chloroethyl)amino]benzoylamino]-ethyl]-5-quinoline-2-carboxamido]indole-2-carboxamide;

N-[2-[4-[N,N-bis(2-chloroethyl)amino]benzoylamino]-ethyl]quinoline-2-carboxamide.

EXAMPLE 5

To a stirred solution of α-bromoacrylic acid (135 mg) and triethylamine (0.125 ml) in dry THF (4 ml) at -10°C, pivaloyl chloride (0.098 ml) was added. Twenty minutes later, the mixture was warmed to room temperature, filtered to remove triethylamonium chloride and then added dropwise to a solution of 5-(benzofuran-2-carboxamido)indole-2-carbohydrazide (150 mg) in dry DMF (5 ml).

The mixture was allowed to stand at room temperature for 1 hour and then poured into 2N hydrochloric acid. The resulting residue was collected and washed with ethanol to give 75 mg of 2'-(α-bromoacryloyl)-5-(benzofuran-2-carboxamido)-indole-2-carbohydrazide;

NMR (DMSO-d6) δ : 6.3 (1H,d); 6.77 (1H,d); 7.2 (1H,bs); 7.2-7.9 (7H,m); 8.12 (1H,bs); 10.3-10.6 (3H,br); 11.7 (1H,bs).

By analogous procedure the following compound were obtained:

2'-(α-bromoacryloyl)-5-(quinoline-2-carboxamido)-indole-2-carbohydrazide,

NMR (DMSO-d6) δ : 6.32 (1H,d); 6.75 (1H,d); 7.10-8.82 (10H,m); 10.12-10.55 (2H,br); 10.6 (1H,s); 11.7 (1H,bs);

5-[5-(α-bromoacryloylamino)indole-2-carboxamido]-indole-2-carboxamide;

N-[2-(α-bromoacryloylamino)ethyl]-5-[benzofuran-2-carboxamido]indole-2-carboxamide;

N-[2-(α-bromoacryloylamino)ethyl]-5-[quinoline-2-carboxamido]indole-2-carboxamide;

N-[2-(α-bromoacryloylamino)ethyl]quinoline-2-carboxamide.

NMR (DMSO-d6) δ :3.0-3.65 (4H, m); 6.15 (1H, d); 6.65 (1H, d); 7.5-8.7 (7H, m); 9.05 (1H, bt)

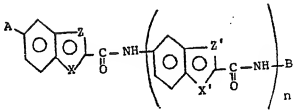
EXAMPLE-6

An injectable pharmaceutical composition can be manufactered by dissolving 1 g of 2'-(α-bromo-acryloyl)-5-(benzofuran-2-carboxamido)indole-2-carbohydrazide in water for injection (1000 ml) and

sealing ampouler of 1-5 ml, in order to prepare an intramuscolar injection of 1 mg/ml.

CLAIMS

1. Heterocyclic oligopeptide derivatives of formula:



(I)

wherein A is hydrogen; $-NHCOR_1$ in which R_1 is an acrylic group substituted in 2-position by halogen, oxiranyl unsubstituted or substituted in 2- or 3-position by a methyl, aziridinyl, cyclopropyl, 4-[N,N-bis-(2-chloroethyl)amino]phenyl, an alicyclic α,β-unsaturated ketone or a lactone;

in which R_2 and R_3 have both the same meaning of C_2-C_4 alkyl group substituted in 2-position by halogen or by a group $-OSO_2R_4$, in which R_4 is C_2-C_4 alkyl or phenyl group, or one of R_2 and R_3 is hydrogen and the other has the meaning as defined above;

B is

hydrogen; $-(CH_2)_m-NHCOR_1$, in which R_1 is as defined above and m has the value of zero or is an integer from 1 to 3;

provided that when A is hydrogen, B is other than hydrogen, and that when A has the other meanings as defined above except hydrogen, B is only hydrogen;

each Z and Z' is, indipendently, -CH= or -CH=CH-;

each of X and X' is, indipendently, N, O or S;

and n is zero or 1; their possible isomers both separately and in mixture: and their pharmaceutically acceptable salts.

2. Heterocyclic oligopeptide derivatives according to claim 1 wherein A is hydrogen; B is $-(CH_2)_m-NHCOR_1$ wherein R_1 is 2-bromoacrylyl, oxiranyl or 4-[N,N-bis(2-chloroethyl)amino]phenyl and m is zero or 2; Z is preferably -CH= when X is oxygen or -CH=CH- when X is nitrogen; Z' is preferably -CH= and X' is nitrogen; n is preferably zero or 1; and their possible isomers and pharmaceutically acceptable salts.

3. Heterocyclic oligopeptide derivatives according to claim 1 wherein A is $-NHCOR_1$ in which R_1 is 2-bromoacrylyl, oxiranyl, 4-[N,N-bis(2-

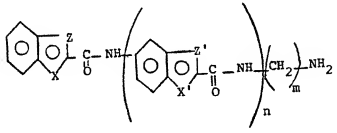
chloroethyl)amino]-phenyl,  in which R_2 and R_3

are the same and when they are a C_2-C_4 alkyl group substituted in 2-position by halogen, they are 2-chloroethyl; Z and Z' are both -CH=; X and X' are preferably both nitrogen; B is hydrogen and n is 1; and their possible isomers and pharmaceutically acceptable salts.

4. 2'-(α-bromoacryloyl)-5-(benzofuran-2-carboxamido)indole-2-carbohydrazide.

5. 2'-[4-(N,N-bis-2'-chloroethylamino-benzoyl]-5-[benzofuran-2-carboxamido]-indole-2-carbohydrazide.

6. A process for the preparation of compounds according to claims 1 to 2 and 4 to 5 wherein A is hydrogen, B is $(CH_2)_n$-$NHCOR_1$, consisting in reacting with a presence of a solvent at a temperature of 20°C to 80°C a compound of formula:

 (II)

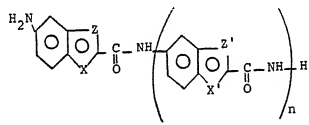
wherein X, X', Z, Z', m and n are as defined above,

with a compound of formula:

(III)

wherein R_1 is as defined above and L represents a leaving group such as halogen like chloride or bromine, an imidazolyl, pivaloyloxy, or isobutyloxycarbonyloxy group; and optionally trasforming into one of their pharmaceutically acceptable salts.

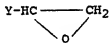
7. A process for preparation of compounds according to claims 1 and 3 wherein A is $-NHCOR_1$ and B is hydrogen, consisting in reacting with a presence of a solvent at a temperature of 20°C to 80°C a compound of formula:



(IV)

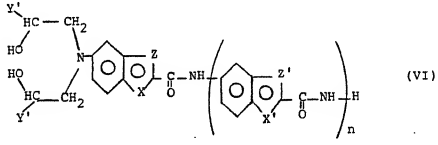
wherein, X, X', Z, Z' and n are as defined above, with a compound of formula III; and optionally transforming into one of their pharmaceutically acceptable salts.

8. Process for preparation of compound according to claim 1 wherein B is hydrogen and A is  in which R_2 and R_3 are as defined above, consisting in reacting, with the presence of a solvent at a temperature of -20°C to 25°C, a compound of formula



(V)

wherein Y is hydrogen or a C_1-C_2 alkyl group, with a compound of formula (IV) to obtain a compound of formula



(VI)

wherein X, X', Z, Z', Y and n are as defined above and Y' has the same meaning of Y; and transforming the compound of formula (VI) into a compound of formula (I) by using an halogenating agent such as

chlorine, bromine, a thionyl halide such as thionyl chloride, sulphonyl halide such as methanesulphonyl chloride; and optionally transforming into one of their pharmaceutically acceptable salts.

9. A process for preparation of compound according to claims 1 to 5 consisting in converting a compound of formula (I) into another compound of the same formula.

10. Intermediate compound of formula II, according to claim 6.

11. Intermediate compound of formula IV, according to claim 7.

12. Intermediate compound of formula VI, according to claim 8.

13. A process according to claims 6 and 7 in which the solvent used is dimethylformamide.

14. A process according to claim 8 wherein the solvent used is methanol.

15. Compounds according to any of claim 1 to 5 usefull against animal and mammalian tumours, such as mammary carcinoma, ovary and endometrial tumors, soft tissue and bone sarcomas, and hematological malignancies, such as leukemias.

16. A pharmaceutical composition comprising heterocyclic oligopeptide derivatives according to

any of claims 1 to 5 in admixture with a pharmaceutically acceptable diluent or carrier.

Amendments to the claims
have been filed as follows

chlorine, bromine, a thionyl halide such as thionyl chloride, sulphonyl halide such as methanesulphonyl chloride; and optionally transforming into one of their pharmaceutically acceptable salts.

9. A process for the preparation of a compound according to any one of claims 1 to 5 consisting in converting a compound of formula (I) into another compound of the same formula.

10. Intermediate compound of formula IV, according to claim 7.

11. Intermediate compound of formula VI, according to claim 8.

12. A process according to claim 6 or 7 in which the solvent used is dimethylformamide.

13. A process according to claim 8 wherein the solvent used is methanol.

14. A compound according to any one of claims 1 to 5 for use in the treatment of an animal or mammalian tumour.

15. A compound according to claim 14, for use in the treatment of a mammary carcinoma, ovary or endometrial tumor, soft tissue or bone sarcoma, or hematological malignancy.

16. A compound according to claim 15, for use in the treatment of a leukemia.

17. A pharmaceutical composition comprising a heterocyclic oligopeptide derivative of formula (I) or salt thereof according to any one of claims 1 to 5 in admixture

with a pharmaceutically acceptable diluent or carrier.

18. A process for the preparation of a compound of formula (I) as defined in claim 1, said process being substantially as hereinbefore described in any one of Examples 1, 3, 4 and 5.

19. A pharmaceutical composition substantially as hereinbefore described in Example 6.

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